



The Impact of Undiagnosed Synaesthesia on the Interpretation of Structural and Functional MRI Images Connectivity Maps and Resulting Diagnoses

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ABSTRACT

Synaesthesia is a condition in which stimulation of a sensory modality triggers another sensation in the alike or an unlike sensory modality. Currently, synaesthesia is deemed a neurological condition that engages unwanted transfer of signals between brain regions from one sense to another “crosstalk activation”. The probability that undiagnosed synaesthesia may impact the results of structural magnetic resonance imaging (MRI), Diffusion Tensor imaging (DTI), functional magnetic resonance imaging (fMRI) and resting state connectivity studies is high, given the multiple anatomical and functional connections within the brain. In this paper, the currently available literature to mark which sensations adjured by synaesthesia and how could this impact MRI different modalities. Our study found that synaesthesia can have an opaque impact on fMRI studies of sensory, memory and cognitive functions, and there is testimony to suggest structural connections in the brain are also mutated DTI measurements especially, it shows enhanced structural connectivity for synesthetes between brain regions, higher Fractional anisotropy (FA), as well as increased in the white matter integrity between some regions.. Given the low dispersal of synaesthesia, the likelihood of synaesthesia being a perplexing factor in DTI, fMRI studies of patient groups is small; however, determining the existence of synaesthesia is paramount for investigating individual patients especially Shizophrenia, and autistic patients.

Indexing terms/Keywords

Synaesthesia, Structural MRI, Diffusion tensor imaging, Functional MRI (fMRI), Resting state fMRI, Brain connectivity.

INTRODUCTION

Synaesthesia, known for sundry hundred years [1]-[4], is a placement in which one kind of stimulation recalls a secondary sensation in the same or different sensory modality (e.g., Synaesthete: each time a he/she visualize a colored text he/she hears sounds, or whenever the rolling stones come on radio, visions of silver triangles appear in his/her head). The anatomy and inter- regional connectivity of the brains of synaesthetes vary from those of non-synaesthetes is reported [5]. Hence, anatomical, structural, or functional studies of the brain may be impacted if they include people with undiagnosed synaesthesia.

Magnetic resonance imaging (MRI) modalities, such as diffusion tensor imaging (DTI) [6] and functional magnetic resonance imaging (fMRI) [7], have been widely adopted to diagnose neurological diseased patients’ in clinical routine by quantifying neurological disrupt through immediate observation of tissue. MRI modalities have the advantage providing high-resolution imaging as well as clear tissue contrast. In addition, they provide no chance of ionizing radiation exposure. Different MRI techniques obtain contrast through their sensitivity to the microstructure of biological tissues; DTI is susceptible to interstitial water diffusion through tissue [6], whereas fMRI is susceptible to changes in blood oxygen levels dependent (BOLD) contrast in response to specific tasks that engage cognitive, motor and sensory processing [7]. DTI and fMRI are serviceable for identifying and assessing neurological disorders; Through, combining these techniques provide extra information about brain arrangement and inter-regional linkage and how these are disrupted in the presence of neurological disease.

More recently, networks of brain regions involved in a task have been identified by cross- correlation analysis of the fluctuations in activity across brain regions during task execution [8]. A significant correlation between regions indicates they are working in synchrony to execute the task; that is, they are functionally connected. Thus, the level of significance of the correlation has been termed functional connectivity. Even more intriguing is the observation that in many cases these same brain regions 40 exhibit significant correlations even when no specific task is being performed (called resting-state connectivity).

Romke et al. [5] have provided a preliminary study using DTI that validates their hypothesis that hyper connectivity causes the added sensations in the synaesthesia and they found an evidence that the increased structural connectivity is associated with the presence of grapheme-color synaesthesia and has a role in the subjective nature of synaesthetic experience. Pathways to see music is shown by Zamm et al. [9], who found that there is a white matter integrity within the right inferior fronto-occipital fasciculus (IFOF) and it was presumedly greater in synesthetes than controls. Furthermore they showed that white matter integrity in synesthetes was correlated with scores on audiovisual experiments of the Synesthesia group especially in the white matter underlying the right fusiform gyrus. Given this potential impact of synaesthesia on the interpretation of DTI and fMRI measurements, this motivates us to undertake a more general study in order to understand the possible impact of synaesthesia on these MRI imaging modalities. Our hypothesis is given that synaesthesia impacts underlying brain structure and brain function, undiagnosed synaesthesia should be considered a general confounding factor in the interpretation of DTI, fMRI and other MRI modalities.

Recently, fMRI has been used to specifically measure brain function and related changes in cognition associated with certain classes of synaesthesia [10]-[13] (see for example, Figure 1). Tomoson et al. reconnoiter functional connectivity of color and grapheme areas during a synesthesia-inducing fMRI paradigm including rest, auditory grapheme stimulation,

and audiovisual grapheme excitation. [14]

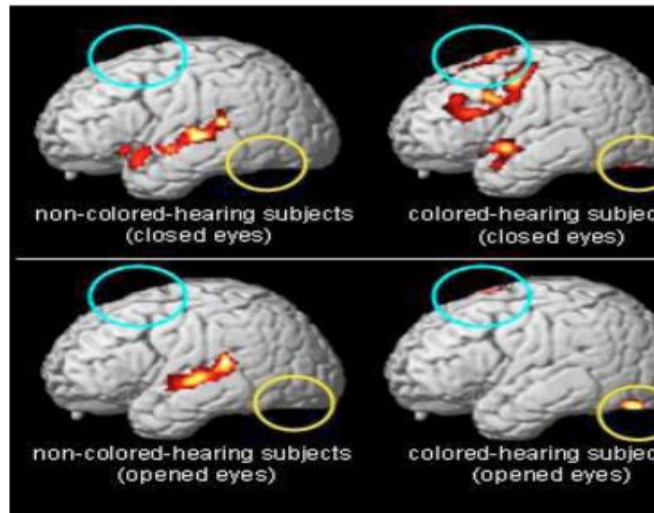


Fig 1: fMRI data illustrating activation of more areas in the brains of synaesthetes compared to normal (adapted from [10]).

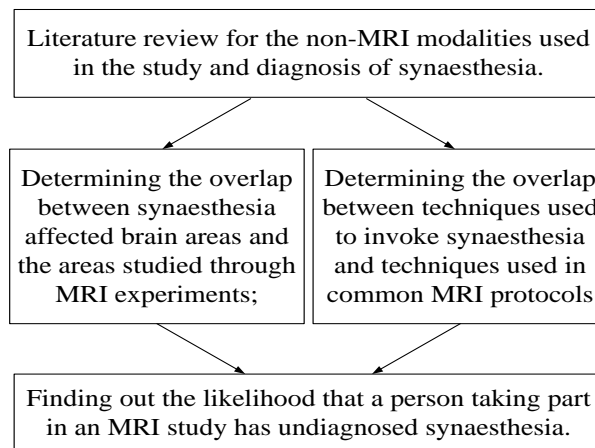


Fig 2: The proposed research methods strategy.

MATERIALS AND METHODS

Data mining was undertaken on the existing literature on the study and diagnosis of synaesthesia using non-MRI modalities, the research used methods are shown in Figure 2. We hoped to determine:

- (i) If brain regions currently recognized as affected by synaesthesia overlap those commonly studied with MRI structural and/or functional imaging;
- (ii) If the experimental techniques used to invoke synaesthesia overlap with techniques used in common fMRI protocols, and
- (iii) The likelihood that undiagnosed/diagnosed synaesthesia impact the interpretation of MRI different modalities data.

RESULTS

Zayed et al. [15] showed the following examples that illustrates the impact of synaesthesia on every day activities:

- (i) Figure. 3A provides a graphic artist's interpretation of how the hearing of sound causes a synaesthete to visualize colored text.
- (ii) Lisa, a synaesthete (graphemes), conveys many crossed associations between letters, numbers, and other symbols in the form of (reshowing) colors, personalities, sexes, and sometimes textures, as seen in Figure. 3B and Table 1.
- (iii) Eagleman et al. [16] stresses that the blending of senses synesthetes experience is not a hallucination. To research this type, they developed a virtual reality program to allow people to place all of their weekdays, months, or numbers into a three- dimensional space and sort them in relationship to their body space. From their research study, synesthesia

appears to be ancestral; the genetic test suggests that colored sequence syhthnesia is linked to a gene in the 16q12.2-23.1 regions.

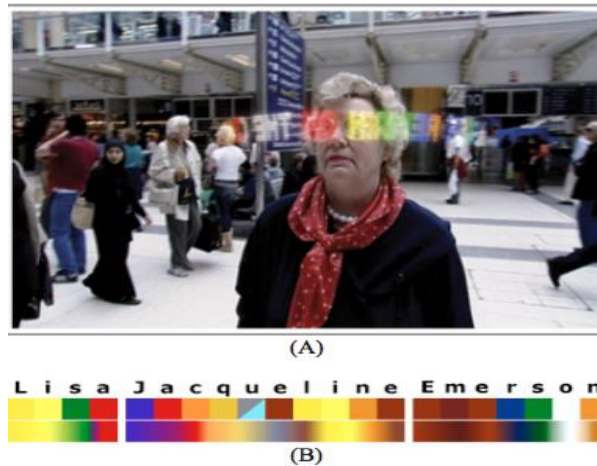


Fig 3: (A) A graphic artist’s interpretation of the reports of projector synaesthete DL, for whom speech produces visualized colored text that is projected into space. (B) An illustration of how a color graphemes synaesthete sees her name as individual letters and as a full word.

The specific colors that appear in response to reading black text on a white background are prevalent across many synaesthetes, suggesting a joint anatomical substrate within the brain. Synaesthetes are equipped with more connections between neurons has been suggested by Baron-Cohen [17], and that the usual pattern of operation in the brain is deviated. We understand this observation has a number of possible MRI and brain connectivity related impacts:

- (i) fMRI tasks may activate more areas in the brain than expected.
- (ii) The increased neural connectivity between synaesthesia connected areas may command to changes in brain tissue characteristics that could appear as different image textures in DTI and affecting the DTI measurements the FA values that indicates the white matter integrity.

The limbic system is primarily responsible for synesthetic experiences are suggested by Cytowic [18]. Since the regulation of emotional responses is uttered by brain structures in the limbic system, then we interpreted that emotional vigilance may spoil feature binding in working memory studies used over and over in fMRI studies, as for example in studies of schizophrenia [19], [20] and Autism [21].

For example, in a post-surgical study of anterior temporal lobectomy, fMRI studies using tasks involving facial and vocal expressions and word recognition, there is also potential for misinterpretation of the results because of the engagement between words and emotional arousal in some synaesthetes [22]. Other example is the impacting that could occur on Alzheimer fMRI experiments [23] where parietal, frontal and occipital–temporal cortical regions and primary visual cortex in the brain are triggered.

Special textures have been reported in MRI images associated with specific gene types present in tumors [24], Eagleman et al. in their research genetic analysis suggests that colored sequence syhthnesia is linked to a gene in the 16q12.2-23.1 regions, and states that synesthesia appears to be heritable. Given its genetic ingredient, it is possible that synaesthesia will also present textures in specific regions of DTI and fMRI images.

Table 1. This table details the plenty of brain responses that occur upon a synaesthete’s reading of black text on a white background. These effects can be expected to confound the interpretation of certain DTI, fMRI, and/or brain connectivity studies. (Synaesthesia Case Study)

Number/ Character	Synaesthete Experience
0	<p>colour: black or white. Unlike the letter ‘o’, which appears white and vanishes from the page, the number ‘0’ “comes in and out of being, so to speak, like it is there and then it isn’t”.</p> <p>sex: male</p> <p>age: in his forties, but also kind of seems ageless in a way</p> <p>personality: intelligent, but keeps himself separated from the others out of a sense of duty.</p>
3	<p>colour: medium-light green</p> <p>sex: female</p> <p>age: not too old, but basically an indefinable age</p>

	personality: grandmotherly and responsible
A	colour: slightly dark red sex: of mixed sex, but mostly female
X	colour: black sex: male

When investigating individual patients, determining the presence of synaesthesia is important. Also fMRI and DTI researchers should be circumspect that reports of synaesthesia are more common amongst certain genetic and gender specific groups. For example, women synaesthetes in the U.S. inhabitance outnumber males by a ratio of 3:1 [25], while a female to male ratio of 8:1 is found in U.K. [26]. Synaesthesia remains basically a self-reported condition, and the confusion of reporting oneself as being “different” may be responsible for the unclear accepted prevalence of synaesthesia in the general inhabitance. Up until recently, synaesthesia was thought to occur in one person out of 25,000; recent assessments range from between 1 in 200 to 1 in 2000 [27] depending on the study performed [28], [29]. Sagiv et al. [30] stated that the estimate concerning the recrudescence of synaesthesia vary widely because the spread estimation was based on the number of people responding to a newspaper advertisement, many cases were probably missed either because they did not see the ad or saw it but choose not to respond. Some researchers think the prevalence (for a mild form) is much higher [27]-[31].

Rocca et al. [32] compared a group of 13 synesthetes with a group of 11 controls. They used the voxel-based morphometry manifesting changes increase in the gray matter volume, looking in the DTI structural parameters of nerve fibres, they find multiple regions of increases FA in synesthetes compared to controls which interpreted as extra visual Functional and structural connections abnormalities [Figure 4].

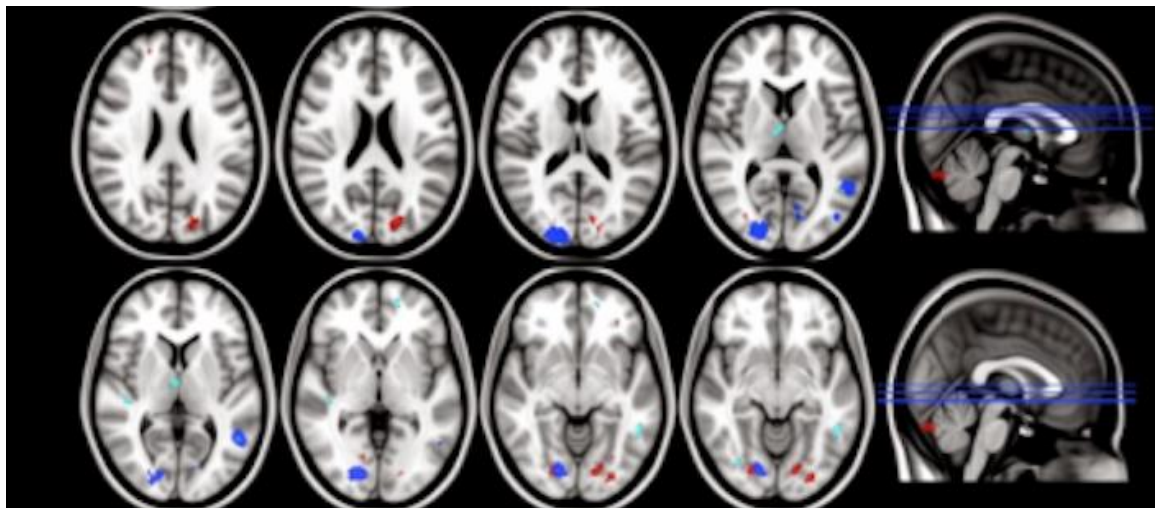


Fig 4: A synaesthete DTI structural parameters, red indicates the grey matter volume increase in the, light blue for increase in white matter volume , dark blue for white matter FA increases (adapted).

In Table 2 we summarize how a number of specific synaesthesia types may impact upon DTI, fMRI, resting state connectivity studies when tasks intended to invoke a specific sensation unintentionally provoke a second sensation.

CONCLUSION

Our data mining exercise on the existing literature, summarized in Figure 5, indicates that fMRI and DTI images and resting state brain connectivity maps may be influenced by changes in brain structure associated with synaesthesia in a number of ways that are not currently recognized in the literature. Given that this effect is well documented, yet probably under-reported because of the social perplexity connected with self diagnosed disease, we leave the reader with two immediate proposal for further technical analysis of how the impact of synaesthesia manifests in DTI and fMRI images. (A) Given the wide range of circumstance under which this type of confounding factor could be detected, it is important that researchers do not set a false positive label on undiagnosed synaesthesia or simply dismiss the effect as noise; and (B) To better understand the prevalence of synaesthesia, a “self report” [33], [34] be added as a simple diagnostic exam for synaesthesia as part of pre or post MRI protocols. In Future researchers may in a hopeful manner tell whether these kinds of cortical deactivations really are an important component of the synaesthetic experience. Meanwhile, our findings add to a multiple different set of neuroimaging findings, which have yet to definitively clinch the neural correlates of the synaesthetic experience. Perhaps expecting a single mechanism is an error, if the condition is really heterogeneous we may need some other means of investigations.

Table 2. The Impact of Synaesthesia Types on DTI, fMRI, and/or Resting state connectivity maps

Synaesthesia Type	First Sensation	The Joint Sensation	Effect in DTI, fMRI, and/or Resting state connectivity maps
Coloured graphemes (66.8%)	Visual	Visual	<p>Significant activity in the cerebral cortex during synesthetic experiences:</p> <p>a) Impacting on Alzheimer fMRI experiments where parietal, frontal and occipital-temporal cortical regions and primary visual cortex in the brain are activated.</p> <p>b) Impacting on resting state connectivity maps for Asperger Syndrome (Autism patients) has been showing more connections in between the visual cortex regions, the same as for Coloured graphemes syntheses which is confused if it is kind of brain plasticity or extra connections shown in the Autism patients to compensate some of the deficits in other functions.</p> <p>c) Impacting on the DTI as it has been shown alterations in the FA values and increase in the white integrity.</p>
Coloured pain (4.4%)	Pain	Visual	
Coloured personalities (4.4%)	Persons	Visual	
Coloured touch (1.9%)	Touch	Visual	<p>a) Since listening to music or certain words can be used in fMRI imaging, then synesthesia may also activated the visual cortex. Also it is confused with the plasticity or the kind of compensation occurs in optic neuritis /multiple sclerosis patients (appears in resting state connectivity maps). b) Impacting on resting state connectivity maps for Asperger Syndrome (Autism patients) as it has been shown more connections in between the visual cortex regions of the autism patients, the auditory areas and other brain regions which is the same as for Coloured general sounds syntheses so it is confusing if it is kind of brain plasticity or extra calltalk connections shown in the Autism patients to compensate some of the deficits in other functions or it may be a generation of an internal sensory in the patients' brain representing deactivation of regions which might compete for attention or provide conflicting information.</p>
Coloured musical sounds (14.5%) Coloured general sounds (12.1%) Vision hearing (1.1%)	Hearing	Visual	
Sound touch (2.7%)	Touch	Sound	
Coloured touch (1.9%) & Vision touch(0.8%)	Touch	Visual	<p>Patients respond by pressing buttons in the fMRI experiments. The cross linkages between touch, sound and vision may introduce unanticipated additional activations</p>

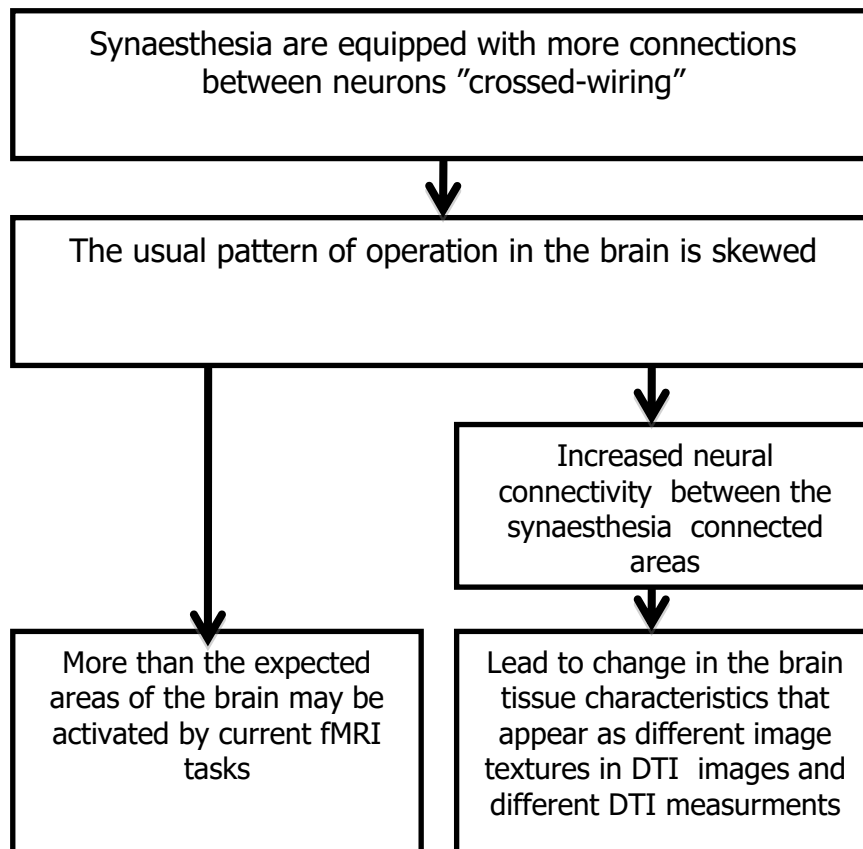


Fig 5: A summary of the impact of synaesthesia on fMRI, DTI, and resting state maps.

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Author' biography with Photo



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